Protocol Number: CRDF-001

A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second-Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma

NCT Number: NCT04752696

Document Date: 18 February 2021

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second-Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma
Protocol Number:	CRDF-001
Study Phase:	2
Product Name:	Onvansertib
IND Number:	153934
Sponsor:	Cardiff Oncology, Inc. 11055 Flintkote Avenue San Diego, CA 92121 [redacted]
Issue Date:	29 January 2021
Version Number:	1.0

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

CONFIDENTIAL

This document and its contents are the property of and confidential to Cardiff Oncology, Inc. (hereinafter referred to as Cardiff Oncology). Any unauthorized copying or use of this document is prohibited.

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL 1
TABLE OF CONTENTS 2
LIST OF TABLES 6
LIST OF FIGURES 6
PROTOCOL APPROVALS 7
INVESTIGATOR SIGNATURE PAGE 8
SYNOPSIS 9
LIST OF ABBREVIATIONS 18
STUDY ADMINISTRATIVE STRUCTURE 20
1 BACKGROUND 21
1.1 Pancreatic Cancer 21
1.2 Onvansertib 22
1.3 Nanoliposomal Irinotecan in Pancreatic Cancer 24
1.4 Rationale 24
1.5 Dose Rationale 24
1.5.1 Rationale for 15 mg/m^2 Onvansertib QD on Day 1 to Day 5 of a 14-day Treatment Cycle 24
1.5.2 Rationale for 12 mg/m^2 Onvansertib QD on Day 1 to Day 10 of a 14-day Treatment Cycle 25
2 STUDY DESIGN OBJECTIVES AND ENDPOINTS 28
2.1 Objectives 28
2.1.1 Primary 28
2.1.2 Secondary 28
2.1.3 Exploratory 28
2.2 Endpoints 28
2.2.1 Primary 28
2.2.2 Secondary 28
2.2.3 Exploratory 29
3 INVESTIGATIONAL PLAN 30
3.1 Overall Study Design and Plan 30
3.1.1 Screening Period 30
3.1.2 Safety Lead-in 30

3.1.2.1 Definition and Management of DLTs 32
3.1.3 Treatment Period 32
3.1.4 End-of-Study 33
3.2 Study Duration 33
4 STUDY POPULATION 34
4.1 Eligibility Criteria 34
4.1.1 Inclusion Criteria 34
4.1.2 Exclusion Criteria 35
4.2 Removal of Patients From Therapy or Assessment 36
5 STUDY DRUG TREATMENT 37
5.1 Description 37
5.1.1 Onvansertib (PCM-075) 37
5.1.1.1 Storage 37
5.1.1.2 Shelf-life 37
5.1.2 Nanoliposomal irinotecan 37
5.1.3 Leucovorin 38
5.1.4 Fluorouracil 38
5.2 Administration 38
5.2.1 Onvansertib Administration 38
5.2.1.1 Food Restrictions 38
5.2.1.2 Dose Rounding 38
5.2.2 Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil Administration 38
5.3 Dose Modifications 39
5.4 Study Drug Inventory and Accountability 40
5.5 Treatment Compliance 40
5.6 Concomitant Medications and Treatments 40
6 STUDY ASSESSMENTS AND PROCEDURES 42
6.1 Schedule of Assessments 42
6.2 Study Procedures 47
6.2.1 Informed Consent and Confirmation of Eligibility Criteria 47
6.2.2 Screening 47
6.2.3 Medical History and Prior Therapy 47
6.2.4 Tumor Biopsy 47

6.2.5 Physical Examinations, Height and Weight, and Vital Signs 47
6.2.6 Eastern Cooperative Oncology Group Performance Status 48
6.2.7 Radiographic Disease Assessment 48
6.2.8 Concomitant Medication Review 48
6.2.9 Adverse Events 48
6.2.10 Electrocardiograms 48
6.2.11 Laboratory Assessments 48
6.2.11.1 Chemistry 48
6.2.11.2 Hematology 49
6.2.11.3 Samples for Pharmacokinetic Analysis 49
6.2.11.4 Samples for Circulating Tumor DNA 49
6.2.12 End-of-Study/Follow-Up 49
7 ADVERSE EVENT REPORTING 50
7.1 Definitions 50
7.1.1 Adverse Event 50
7.1.2 Unexpected Adverse Events 50
7.1.3 Serious Adverse Event 50
7.2 Severity of Adverse Events 51
7.3 Relationship of Adverse Events to the Study Drug 51
7.4 Monitoring of Adverse Events 51
7.5 Reporting Procedures 52
7.5.1 Routine Reporting of Adverse Events 52
7.5.2 Reporting of Serious Adverse Events, Including Death 52
7.5.3 Other Events Requiring Immediate Reporting 54
7.5.3.1 Overdose 54
7.5.3.2 Pregnancy 54
8 PATIENT DISCONTINUATION AND TRIAL DISCONTINUATION 55
8.1 Patient Discontinuation 55
8.2 Study Discontinuation 55
9 STATISTICAL METHODS 56
9.1 Determination of Sample Size 56
9.2 Statistical Considerations 56
9.3 Statistical Analysis 56

9.3.1 Statistical Analysis of Safety Data....56
9.3.2 Statistical Analysis for Efficacy Data....56
9.3.3 Statistical Analysis for Pharmacodynamics and Biomarkers....56
10 ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS....58
11 QUALITY CONTROL AND QUALITY ASSURANCE....59
11.1 Data Collection....59
11.2 Study Monitoring....59
11.3 Data Management....59
11.4 Sponsor Audits....60
11.5 Inspection by Regulatory Authorities....60
12 ETHICS....61
12.1 Declaration of Helsinki....61
12.2 Good Clinical Practice and Regulatory Compliance....61
12.3 Institutional Review Board/Independent Ethics Committee....61
12.4 Informed Consent....61
12.5 Emergency Departure from Protocol....62
13 PUBLICATION POLICY....63
14 PROTOCOL AMENDMENTS AND MODIFICATIONS....64
15 REFERENCES....65
16 APPENDICES....67
16.1 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0....68
16.2 Eastern Cooperative Oncology Group Performance Status....69

LIST OF TABLES

Table 1 Summary of Mean Inhibitor Potency of Onvansertib for Human Liver Cytochrome P450s 23
Table 2 Simulated Onvansertib Pharmacokinetic Results With Different Dose and Dosing Regimens 27
Table 3 Definitions for Adequate Organ and Bone Marrow Function 35
Table 4 Dose Levels of Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil 39
Table 5 Dose Reduction Levels of Study Drugs 39
Table 6 Schedule of Assessments 43

LIST OF FIGURES

Figure 1 Onvansertib Concentration Over Time in the Colorectal Cancer Trial 25
Figure 2 Neutrophil and Platelet Counts in Over Time in the Metastatic Castration-resistant Prostate Cancer Trial 26
Figure 3 Safety Lead-in Flow Chart 32

PROTOCOL APPROVALS

A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma

PROTOCOL APPROVAL SIGNATURES
Cardiff Oncology, Inc.

[redacted]

[redacted]
Title

2/18/2021
Date

[redacted]

[redacted]
Title

2/18/2021
Date

INVESTIGATOR SIGNATURE PAGE

Protocol No: CRDF-001
Protocol Version: 1.0
Protocol Date: 29 January 2021
Protocol Title: **A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma**

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the Clinical Study.

I will provide copies of the protocol to the Investigational Review Board (IRB) and all members of the Study team responsible to me who participate in the Study. I will discuss this material with them to ensure that all participating personnel at the Study site are fully informed regarding the investigational drug and the conduct of the protocol.

Once the IRB approves the protocol, I will not modify this protocol without obtaining the prior approval of both the Sponsor and the IRB. I will submit the protocol modifications and/or any modifications to the Informed Consent Form to the Sponsor and the IRB, as applicable, and approval will be obtained before any modifications are implemented.

Investigator's Signature	Date
Investigator's Printed Name	
Study Site Name	
Address	
City, State, Zip Code, Country	

SYNOPSIS

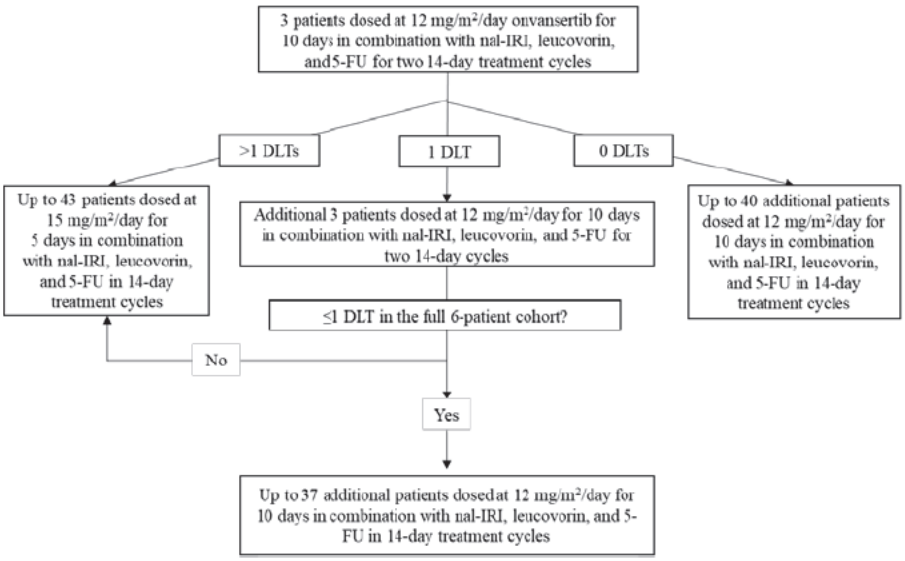
Protocol Title:	A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma
Protocol Number:	CRDF-001
IND Number:	153934
Number of Study Sites:	This study will be conducted at 6 study centers in the United States
Phase:	2
Principal Investigator:	Daniel Ahn, DO
Objectives:	**Primary:** To assess the efficacy of onvansertib in combination with nanoliposomal irinotecan (nal-IRI), leucovorin, and fluorouracil (5-FU) for treatment of patients with histologically confirmed metastatic pancreatic ductal adenocarcinoma (PDAC) who have failed first line gemcitabine-based therapy **Secondary:** • To determine the overall survival (OS) of patients with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5-FU • To determine the duration of response (DOR) of patients with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5-FU • To assess the frequency and severity of adverse events (AEs) in patients with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5-FU **Exploratory:** • To identify biomarkers related to sensitivity and resistance to treatment using patient-derived organoids, blood samples, and archival tissue biopsies. • To assess KRAS allelic burden through serial collection of circulating tumor DNA (ctDNA) and to identify blood-based biomarkers related to: (a) de novo sensitivity and (b) tumor evolution and resistance
Regimen, Dose, Scheduling and Mode of Administration:	One treatment cycle is 14 days. **Onvansertib:** **Once Daily (QD) on Day 1 to Day 10 of a 14-day treatment cycle:** • Patients will receive onvansertib 12 mg/m^2/day, orally (PO) **OR** **QD on Day 1 to Day 5 of a 14-day treatment cycle:** • Patients will receive onvansertib 15 mg/m^2/day, PO

	nal-IRI, leucovorin, and 5-FU (administered sequentially): **On Day 1 of a 14-day treatment cycle:** • nal-IRI 70 mg/m^2 (50 mg/m^2 in patients homozygous for UGT1A1*28), continuous IV infusion for 90 minutes • Leucovorin 400 mg/m^2, continuous IV infusion for 30 minutes • 5-FU 2400 mg/m^2, continuous IV infusion for 46 hours
Study Design:	This is a multicenter, open-label, single-arm study to assess the safety and preliminary efficacy of onvansertib in combination with nal-IRI, leucovorin, and 5-FU as a second-line treatment in patients with metastatic PDAC. Patients with PDAC must have histologically confirmed measurable and metastatic disease for study eligibility. In addition, patients must have failed treatment with one line of gemcitabine-based prior chemotherapy. This study will consist of a Screening Period, a Safety Lead-in, a Treatment Period conducted in 14-day cycles, End-of-Study (EOS) evaluations, and a Follow-Up Period. The purpose of the Safety Lead-in is to assess the safety and tolerability of a modified onvansertib dose, and dosing schedule of 12 mg/m^2 QD for 10 days (Day 1 to Day 10) of a 14-day treatment cycle. The safety and tolerability of the onvansertib 15 mg/m^2 QD for 5 days (Day 1 to Day 5) of a 14-day treatment cycle has been previously established. The recommended dose and regimen (either 12 mg/m^2 QD for 10 days in a 14-day treatment cycle or 15 mg/m^2 QD for 5 days in a 14-day treatment cycle) for the study will be determined in the Safety Lead-in based on the overall safety profile of each dose and dosing regimen, including dose-limiting toxicities (DLTs), drug modifications and reductions, and AEs. Patients will continue treatment in this study (Cycle 1, Cycle 2, Cycle 3, etc.) until disease progression (PD) or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Prior to the start of each treatment cycle, patients will have blood samples drawn for hematology (see Section 6 for Schedule of Assessments). Only patients with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L will continue with study treatment for that cycle; patients not meeting this threshold will resume treatment when these criteria are met. Other non-hematological lab parameters should be within range per eligibility criteria (as defined in Table 3). Local site-specific COVID-19-related procedures will be implemented to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the study. Screening Period Within 28 days prior to the first onvansertib dose, Screening assessments will be performed, as outlined in the Schedule of Assessments (Table 6). Key assessments at Screening include medical history (including a thorough review and recording of significant past medical and surgical history, current conditions, concomitant therapies, and TNM stage [tumor, nodes, metastasis]

	at diagnosis), prior and concomitant medications, and baseline radiographic scans. Safety Lead-in The purpose of the Safety Lead-in is to assess the safety and tolerability of a modified dose and dosing schedule for onvansertib. Three patients will initially be enrolled in the Safety Lead-in. On Day 1 of the first 2 cycles for the initial 3 patients in the Safety Lead-in, onvansertib will be administered PO QD at a dose of 12 mg/m^2 for 10 days (Day 1 to Day 10) of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. The DLT evaluation period is the first two 14-day cycles of treatment plus an additional 2 weeks for any hematologic DLTs to resolve to Grade 2 or less or any nonhematologic DLT to resolve to Grade 1 or less. Any Grade $\geq$ 3 adverse event, irrespective of drug attribution, is considered a DLT. At the end of the DLT evaluation period, safety data for the initial 3 patients will be reviewed by the Investigators and the Sponsor for evaluation of DLTs (see bulleted list below) or other safety events determined by the Investigators and Sponsor to be unacceptable. Depending on the results, the Safety Lead-in cohort may be expanded, or dosing of all subsequent patients in the trial will commence (see Synopsis Figure 1): • If no DLTs occur in the 3 first patients at a dose of 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) of the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, then dosing may begin for all subsequent patients at 12 mg/m^2 for 10 days (Day 1 to Day 10) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 40 additional patients would be enrolled. • If 1 DLT is observed in the first 3 patients at a dose of 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) in the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, an additional 3 patients may be enrolled with the same dosing schedule, if deemed safe by the Sponsor and Study Investigators. If no further DLTs occur in these 3 additional patients, dosing may begin for all subsequent patients at 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 37 additional patients would be enrolled to receive 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. However, if any further DLTs are observed in the 3 additional patients receiving 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU, then all subsequent patients will be dosed at 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 43 patients would be enrolled at the 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU.

- If >1 DLT is observed in the first 3 patients at a dose of 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) in the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, then all subsequent patients will be dosed at 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 43 patients would be enrolled at the 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) in combination with nal-IRI, leucovorin, and 5-FU.

Synopsis Figure 1: Safety Lead-in Flow Chart



5-FU=fluorouracil; DLT=dose-limiting toxicity; nal-IRI=nanoliposomal irinotecan.

Treatment Period

Treatment will commence with the onvansertib dose selected based on the results of the Safety Lead-in (either 15 mg/m^2 on Day 1 to Day 5 of each 14-day treatment cycle or 12 mg/m^2 on Day 1 to Day 10 of each 14-day treatment cycle) in combination with nal-IRI 70 mg/m^2 (50 mg/m^2 in patients homozygous for UGT1A1*28), leucovorin 400 mg/m^2, and 5-FU 2400 mg/m^2 administered on Day 1 of each 14-day treatment cycle (Synopsis Table 1).

Synopsis Table 1: Study Drug Doses

Drug	Dose	Frequency
Onvansertib	12 mg/m^2 PO **OR** 15 mg/m^2 PO	QD on Days 1-10 of each 14-day cycle **OR** QD on Days 1-5 of each 14-day cycle

	<table><tr><td>**Nanoliposomal irinotecan**</td><td>70 mg/m^2 (50 mg/m^2 in patients homozygous for UGT1A1*28) Continuous IV infusion for 90 minutes</td><td>Day 1 of each 14-day cycle</td></tr><tr><td>**Leucovorin**</td><td>400 mg/m^2 Continuous IV infusion for 30 minutes</td><td>Day 1 of each 14-day cycle</td></tr><tr><td>**Fluorouracil**</td><td>2400 mg/m^2 Continuous IV infusion for 46 hours</td><td>Beginning on Day 1 of each 14-day cycle</td></tr></table> Abbreviations: IV=intravenous; PO=orally; QD=once daily. Dose adjustments for onvansertib, nal-IRI, leucovorin, and 5-FU are allowed in accordance with Section 5.3; additional details for nal-IRI, leucovorin, and 5-FU are provided in the relevant package inserts. Radiographic imaging during the Treatment Period will be obtained every 8 weeks, prior to the start of Cycles 5, 9, 13, 17, etc. until EOS as outlined in the Schedule of Assessments (Table 6). Radiographic imaging should include computed tomography (CT) of the chest/abdomen/pelvis with contrast (or magnetic resonance imaging [MRI] if patient has contraindication to intravenous contrast). End-of-Study EOS evaluations should occur within 28 days (± 5 days) of the last administered dose of onvansertib. Follow-Up After completion of treatment, subjects will be followed every 2 months for PD and survival for up to 1 year. Follow-up information can be collected via voice or written contact.
Sample Size:	Up to 43 patients
Endpoints:	Primary Overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Secondary • Treatment safety based on toxicities evaluated according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 in patients who have received at least one dose of onvansertib • Duration of response (DOR) • ORR in patients who receive ≥ 2 treatment cycles of onvansertib, nal-IRI, leucovorin, and 5-FU • Median overall survival (OS)

	• Disease control rate (DCR; defined as CR, PR or stable disease [SD]) by RECIST v1.1 over the entire Treatment Period • Reduction (≥50% from baseline) in serum CA 19-9 response Exploratory • Establishment of patient-derived organoids from tissue biopsies to perform pharmacosensitivity, genomic and transcriptomic analyses, and identify biomarkers associated with treatment response • Genomic profiling of ctDNA at baseline and PD to identify genomic markers associated with patient sensitivity and resistance to treatment • Use of archived tumor tissue biopsy samples (if available) to evaluate genomic profiles (DNA/RNA) associated with patient response • Assessment of KRAS allelic burden in liquid biopsies as measured by circulating tumor DNA (ctDNA)
Indication:	Second-line treatment of histologically-confirmed, metastatic PDAC
Diagnosis and Eligibility Criteria:	Patients who meet all of the following Inclusion Criteria and none of the Exclusion Criteria will be eligible to be enrolled in the study. **Inclusion Criteria:** 1. Histologically or cytologically confirmed metastatic PDAC 2. Has received 1 prior gemcitabine-based chemotherapy as first-line therapy for metastatic disease. Progression after completion of neoadjuvant or adjuvant therapy of < 6 months in duration is considered 1 line of therapy for metastatic disease 3. Has measurable disease according to RECIST v1.1, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan 4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 5. Must be willing and able to undergo a tissue biopsy at screening; patients who, in the opinion of the investigator, do not have tissue that is accessible for biopsy are excepted from this criterion 6. Women of childbearing potential: (defined as not post-menopausal for 12 months or no previous surgical sterilization) and fertile men must agree to use adequate contraception for the duration of study participation and for 4 months after the last dose of nal-IRI. Male subjects must agree to refrain from sperm donation during the study and for 4 months after the last dose of nal-IRI 7. Ability to understand and the willingness to sign a written informed consent document. Signed informed consent form must be obtained prior to initiation of study evaluations and/or activities 8. International Normalized Ratio (INR) < 1.5 unless on warfarin

9. Patients with prior malignancy and treated with no evidence of active disease more than 2 years from initial diagnosis are eligible
10. Age ≥ 18 years.
11. Patients must have adequate organ and marrow function as defined in Synopsis Table 2

Synopsis Table 2: Acceptable Organ Function

ALT and AST	≤ 3 × institutional ULN OR ≤ × 5 ULN in presence of liver metastases
Bilirubin	≤ ULN
Creatinine	≤ 1.5 × ULN or creatinine clearance > 50 ml/minute as calculated by the Cockcroft-Gault equation
HGB	≥ 9.0 g/dL
ANC	≥ 1.5 × 10^9/L
PLTs	≥ 100 × 10^9/L

Abbreviations: ANC=absolute neutrophil count; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HGB=hemoglobin; PLTs=platelets; ULN=upper limit of normal.

Exclusion Criteria:

Patients eligible for this study must not meet any of the following criteria:

1. Prior treatment with irinotecan, nal-IRI or an investigational Polo-like kinase-1 (PLK1) inhibitor
2. Uncontrolled intercurrent illness including symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, and myocardial infarction within 3 months of initiation of therapy.
3. History of interstitial pneumonitis or interstitial lung disease
4. Patients with microsatellite instability-high (MSI-H) tumors with no prior immune checkpoint inhibitor exposure
5. Pregnancy or lactation
6. Patient has active and uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy
7. QT interval with Fridericia's correction (QTcF) > 470 milliseconds. The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation, (eg, medications, hypokalemia), the triplicate ECG may be repeated once during Screening and that result may be used to determine eligibility

	8. Planned concomitant use of medications known to prolong the QT/QTc interval 9. Patient has undergone major surgical resection within 4 weeks prior to enrollment 10. Patient received radiotherapy, surgery, chemotherapy, or an investigational therapy within 2 weeks prior to study entry 11. Patient has serious medical risk factors involving any of the major organ systems such that the investigator considers it unsafe for the patient to receive an experimental research drugs 12. Serious psychiatric or medical conditions that could interfere with treatment 13. Major bleeding in the last 4 weeks 14. More than one prior chemotherapy regimen administered in the metastatic setting 15. Unable or unwilling to swallow oral medication 16. Use of strong CYP or UGT1A1 inhibitors or strong CYP inducers. Patients currently receiving these agents who are able to switch to alternate therapy are not excluded. Inhibitors should be stopped at least one week prior to the first dose of protocol therapy and inducers should be stopped at least two weeks prior to initiation of protocol therapy
Efficacy Evaluation:	Patients will have response assessment (RECIST v1.1) by CT scan at 8-week intervals. Following each CT scan, only patients with disease control, defined as complete response, partial response or stable disease, will continue on treatment until PD (defined by RECIST v1.1), death, intolerance, withdrawal of consent, or inter-current illness. When any of these criteria are met, the patient will be removed from the protocol treatment.
Safety Evaluation:	Toxicity will be graded using the NCI-CTCAE version 5.0 (Appendix 16.1). • Safety analyses will be conducted on all patients who have received at least 1 dose of any of the study drugs, and will include the frequency of all AEs and laboratory abnormalities, and the frequency of dose interruptions, dose reductions, and treatment discontinuations. • Additional safety assessments will include physical examination, medical history, ECOG performance status, weight, vital signs measurements, and clinical laboratory testing.
Pharmacodynamic and Correlative Biomarker Evaluation:	A tumor biopsy will be performed in all patients during screening for the establishment of patient-derived organoids; patients who, in the opinion of the investigator, do not have tissue that is accessible for biopsy are excepted from this mandatory biopsy.

	Blood samples for pharmacodynamic analyses and genomic profiling will be collected at pre-defined time points pre- and post-administration of onvansertib, nal-IRI, leucovorin, and 5-FU as outlined in the Schedule of Assessments (Table 6).
Statistical Methods:	**Safety Analysis** Safety assessment data for all subjects who receive at least 1 dose of any of the study drugs will be listed and summarized and will include data from AEs and concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, and clinical laboratory testing values. Descriptive statistics will be generated as appropriate (eg, mean, median, range, and standard deviation for continuous data; and frequency for categorical data). **Efficacy Analysis** Subjects who had received at least 1 cycle of onvansertib in combination with nal-IRI, leucovorin, and 5-FU will be included in the treated-patient population efficacy analysis (Table 6). Descriptive statistics will be generated as appropriate (eg, mean, median, range, and standard deviation). Median survival and PFS statistics will be estimated using the Kaplan-Meier method. **Pharmacodynamic Analysis** Circulating tumor DNA isolated from serial blood samples will be used to monitor changes in KRAS mutant allelic frequency during treatment and will be correlated with patient response. Genomic profiles (RNA and/or DNA) will be performed on ctDNA, patient-derived organoids, and biopsy tissue (if available) to evaluate biomarkers correlated with patient response. Pharmacosensitivity to onvansertib, nal-IRI, leucovorin, and 5-FU will be assessed in patient-derived organoids and correlated to treatment response.
Sample Size Rationale	The total planned sample size is up to 43 patients. The primary efficacy endpoint is ORR by RECIST v1.1. The primary endpoint will be tested and a Fleming single-stage design will be used. The null hypothesis for ORR that the true ORR is 7.7% will be tested against a one-sided alternative of 20% ORR. The null hypothesis on ORR will be rejected if 6 or more responses are observed in the first 39 evaluable patients. For the primary endpoint, the sample size will provide 80% power to reject the alternative hypothesis with type I error rate of 0.1 (actual error rate of 0.076; PASS 14 Power Analysis and Sample Size Software v14.0.05). Evaluable patients are defined as those who receive at least 1 cycle of onvansertib in combination with nal-IRI, leucovorin, and 5-FU. Four additional patients will be enrolled to take into account ineligibility, withdrawals, etc.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BOR	Best overall response
CBC	Complete blood count
CFR	Code of Federal Regulations
CR	Complete response
CRC	Colorectal cancer
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End-of-Study
5-FU	fluorouracil
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IND	Investigational new drug
IRB	Institutional Review Board
MSI-H	Microsatellite Instability High
MRI	Magnetic resonance imaging
nal-IRI	Nanoliposomal irinotecan
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Disease progression
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-free survival
PI	Package Insert; Prescribing Information
PK	Pharmacokinetic(s)
PLK	Polo-like kinase
PO	Orally
PR	Partial response
QD	Once daily
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
TNM	Tumor, node, metastasis
US	United States

STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator:	[redacted]
Contract Research Organization:	PRA Health Sciences
Medical Monitor:	TBD

1 BACKGROUND

1.1 Pancreatic Cancer

Pancreatic cancer remains the most lethal cancer with less than 6% five-year overall survival across all stages and despite recent advances with the advent of gemcitabine and nab-paclitaxel or FOLFIRINOX.[1,2,3,4] It is the 4th most deadly cancer in the Western world and is poised to become the second most deadly by 2030.[4] There is an urgent need to improve treatment of patients with current and emerging therapeutic strategies. In the metastatic setting, FOLFIRINOX and nab-paclitaxel-gemcitabine are standard treatment options in patients with good performance status (Eastern Cooperative Oncology Group [ECOG] 0/1). Both combinations have shown a survival advantage over previously standard gemcitabine monotherapy, with 11.1 months overall survival (OS) for FOLFIRINOX and 8.7 months for nab-paclitaxel-gemcitabine versus ~6.7 months for gemcitabine alone.[2, 3]

Most pancreatic cancers progress within a few months during or after first-line chemotherapy, and an unmet need remains for second-line treatment. Recently, nanoliposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and leucovorin was approved for second-line treatment of metastatic pancreatic ductal adenocarcinoma (PDAC) in patients who received prior gemcitabine treatment. In the Phase 3 study NAPOLI-1, the combination of nal-IRI plus 5-FU/leucovorin conferred a significant improvement in outcome over 5-FU/leucovorin, with a response rate of 16% (vs. 1%), progression-free survival (PFS) of 3.1 months (vs. 1.5 months) and OS of 6.1 months (vs. 4.2 months).[5]

KRAS is the most common oncogene mutated in pancreatic adenocarcinoma, and it is mutated in nearly all tumors.[6,7,8] Mutant KRAS is essential for PDAC growth, where the constitutive activated RAS proteins contribute to tumorigenesis, treatment resistance, and metastases.[6]

Despite research and drug development efforts focused on KRAS, no effective RAS inhibitors have been approved for the treatment of pancreatic cancer with KRAS mutation. The poor prognosis of KRAS-mutated PDAC patients and the absence of KRAS-targeted therapies, highlight the urgency to develop novel therapies aimed at KRAS.

Polo-like kinase (PLK) 1 is the most well-characterized member of the family of serine/threonine protein kinases and strongly promotes the progression of cells through mitosis. PLK1 performs several important functions throughout the mitotic phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome inhibitors, and the regulation of mitotic exit and cytokinesis.[9] PLKs also have roles in DNA replication and cellular responses to DNA damage. PLK1 is ubiquitously expressed in normal proliferating tissues and is aberrantly overexpressed in a wide variety of human tumors. The over-expression of PLK1 in solid tumors indicates poor prognosis.[10,11,12]

PLK1 inhibition results in the arrest of cell division and subsequent cell death. PLK1 inhibition resulted in the impairment of viability of several KRAS mutated cell lines and xenografts, and

tumor cells with mutations in TP53 are more sensitive to PLK1 inhibition.[9,13,14] These findings suggest targeting PLK1 to be an appealing target in pancreatic cancer where treatment options in the second-line setting are limited.

1.2 Onvansertib

Onvansertib (also known as PCM-075 and NMS-1286937) is the first PLK1-specific adenosine triphosphate competitive inhibitor administered by oral route to enter clinical trials with proven antitumor activity in different preclinical models. The compound shows high potency in proliferation assays and has low nanomolar activity against a large number of cell lines from both solid and hematologic tumors. Onvansertib potently causes mitotic cell-cycle arrest, followed by apoptosis in cancer cell lines, and inhibits xenograft tumor growth with a clear PLK1-related mechanism of action at well-tolerated doses in mice after oral administration. Onvansertib has favorable pharmacologic parameters and good oral bioavailability in rodent and nonrodent species. In addition, onvansertib has proven antitumor activity in different nonclinical models using a variety of dosing regimens, which may provide flexibility in dosing schedules, and therefore, warrants investigation in clinical settings.

The major metabolic pathways found in the different animal species were N-oxidation of the N-methyl piperazine ring to give N-oxide M2 and hydroxylation on an aliphatic carbon atom of the methylene bridge of the pyrazoloquinazoline moiety to give metabolite M1. Qualitatively, no marked differences in the metabolism of onvansertib were observed between species and, quantitatively, some differences were observed cross-species.

The potential inhibitory capacity of onvansertib towards the major human cytochrome P450 (CYP) isoforms that are responsible for hepatic drug metabolism in man (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated using human liver microsomes. Onvansertib was able to inhibit the metabolic activities of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isoforms to different extents, with 50% inhibitory concentration (IC_{50}) values ranging from 20 µM to 66 µM (Table 1). No significant inhibitory effects against CYP1A2 were detected. Considering that the concentrations relevant to achieve significant anti-tumoral activity of the compound in mice were in the order of 1 µM, the likelihood that onvansertib would show clinically relevant metabolic drug-drug interactions is considered low.

Table 1 Summary of Mean Inhibitor Potency of Onvansertib for Human Liver Cytochrome P450s

P450 Enzyme	Enzyme Reaction	IC_{50} (μM)[a]
CYP1A2	Tacrine 1-hydroxylation	> 100
CYP2C8	Paclitaxel 6-hydroxylation	20.2 ± 1.6
CYP2C9	Diclofenac 4-hydroxylation	20.4 ± 3.2
CYP2C19	Mephenytoin 4-hydroxylation	36.9 ± 15.7
CYP2D6	Bufuralol 1-hydroxylation	26.8 ± 5.4
CYP3A4	Testosterone 6β-hydroxylation	52.7 ± 9.8
CYP3A4	Midazolam 1'-hydroxylation	66.2 ± 4.0

Source: Report No. 0204-2007-R
Abbreviations: IC_{50}=50% inhibitory concentration; SEM=standard error of mean.
[a] Data are mean ± SEM.

Onvansertib has been evaluated preclinically in combination with several different chemotherapies, including irinotecan, cisplatin, cytarabine, doxorubicin, gemcitabine and paclitaxel, and with targeted therapeutics such as abiraterone, histone deacetylase inhibitors, fms-like tyrosine kinase 3 inhibitors, and bortezomib. These therapies are used clinically for the treatment of many hematologic and solid cancers, including acute myeloid leukemia, non-Hodgkin's lymphoma, PDAC, metastatic colorectal cancer (CRC), metastatic castration-resistant prostate cancer, adrenocortical carcinoma, triple negative breast cancer, small cell lung cancer (SCLC), and ovarian cancer. In a Phase 1 safety study with onvansertib has been completed in adult patients with advanced/metastatic solid tumors.[15] After further cohort expansion, the maximum tolerated dose was determined to be 24 mg/m^2/day. The best observed treatment response was stable disease (SD); SD occurred in 5 of the 16 evaluable patients (1 of these patients had PDAC). The study identified thrombocytopenia and neutropenia as the primary toxicities; this is consistent with the expected mechanism of action of onvansertib and with results from the preclinical studies. These hematologic toxicities were reversible, with recovery usually occurring within 3 weeks.

Two additional clinical studies of onvansertib in solid tumor cancers are currently ongoing as follows: Study TROV-053 (A Phase 2 Study of Onvansertib in Combination with Abiraterone and Prednisone in Subjects with Metastatic Castration-Resistant Prostate Cancer [mCRPC]; NCT03414034), and Study TROV-054 (A Phase 1b/2 Study of Onvansertib in Combination with FOLFIRI and Bevacizumab in Subjects with KRAS-mutated Metastatic Colorectal Cancer [mCRC]; NCT03829410).

Additional details regarding the nonclinical and clinical studies of onvansertib are provided in the onvansertib Investigator's Brochure.

1.3 Nanoliposomal Irinotecan in Pancreatic Cancer

Nanoliposomal irinotecan (nal-IRI) comprises irinotecan free-base encapsulated in liposome nanoparticles.[16] The liposome is designed to keep irinotecan in the circulation sheltered from conversion to the active metabolite SN-38 longer than free (unencapsulated) irinotecan. This increases and prolongs intratumoral levels of both irinotecan and SN-38 compared with free irinotecan.

Clinically, the combination of nal-IRI plus 5-FU/leucovorin conferred a significant improvement in outcome over 5-FU/leucovorin,[5] and is now considered a standard and approved second line regimen in metastatic PDAC patients who received gemcitabine-based treatment in first line. Studies to establish a role for the combination in first line are underway.

1.4 Rationale

PLK1 inhibition is a potential target in KRAS-mutated pancreatic cancer and may provide a new second-line treatment option. The synergistic activity observed between irinotecan and onvansertib and 5-FU and onvansertib in preclinical KRAS mutant CRC models resulted in an ongoing Phase 1b/2 clinical trial in patients with KRAS mutant metastatic CRC.[17] As of 20 August 2020, in the Phase 1b segment of this trial, 10 of 11 (91%) patients had clinical benefit (partial response [PR] or stable disease [SD]) at 8 weeks. Five (45%) patients achieved a PR ($\geq$ 30% tumor shrinkage), including 4 patients with a confirmed PR and 1 patient going on to curative surgery; 1 patient with an initial PR went off study prior to confirmatory scan due to non-treatment related event. Eight (73%) patients had durable responses of > 6 months (range 6 to > 12 months); 4 patients remain on treatment; median PFS has not yet been reached; only 1 patient progressed in < 6 months while on treatment.

Based on the rationale and early clinical findings, we propose this Phase 2 study to evaluate onvansertib in combination with nal-IRI, leucovorin, and 5-FU for the treatment of patients with metastatic PDAC in the second-line setting.

1.5 Dose Rationale

1.5.1 Rationale for 15 mg/m^2 Onvansertib QD on Day 1 to Day 5 of a 14-day Treatment Cycle

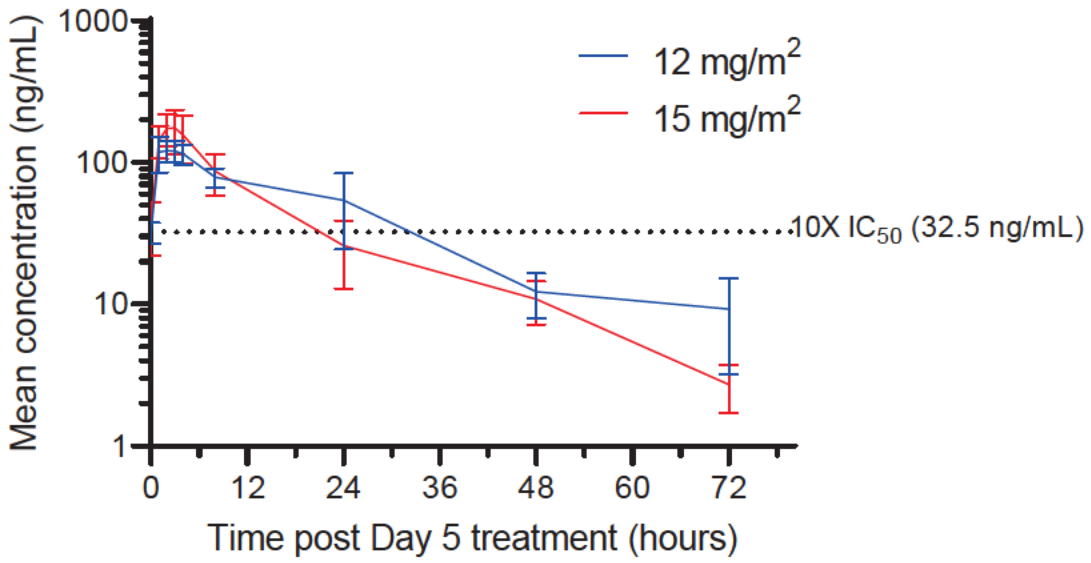
The dose and schedule of 15 mg/m^2 onvansertib on Day 1 to Day 5 of each 14-day treatment cycle was selected based on analysis of pharmacokinetic (PK), pharmacodynamic, safety, and efficacy data from the ongoing Phase 1b/2 clinical study in KRAS-mutated metastatic CRC. In the ongoing Phase 1b for metastatic CRC patients, the combination treatment has been cleared for safety at onvansertib dose levels of 12 mg/m^2 and 15 mg/m^2. The only Grade 3 or 4 hematological event reported at those dose levels has been neutropenia, reported in 4 of the 9 patients treated. The 5-FU bolus was removed from the regimen of those 4 patients and no additional event of Grade 3-4 neutropenia was reported thereafter, indicating that the 5-FU bolus was the cause of neutropenia. Considering that the 5-FU bolus is not part of the chemotherapy regimen of PDAC patients, it is

expected that onvansertib 12 mg/m^2 or 15 mg/m^2 in combination with nal-IRI, leucovorin, and 5-FU will be well tolerated with no high-grade hematological toxicities.

1.5.2 Rationale for 12 mg/m^2 Onvansertib QD on Day 1 to Day 10 of a 14-day Treatment Cycle

The dose and schedule of 12 mg/m^2 onvansertib on Day 1 to Day 10 of each 14-day treatment cycle is proposed to increase the exposure time to onvansertib and optimize efficacy. Based on PK data from the Phase 1b CRC study, onvansertib concentration dropped below its effective level threshold (10 × the IC_{50} to account for effects of plasma protein binding) by Day 7 (48 hours after onvansertib last dose; Figure 1), indicating that the tumor is not exposed to onvansertib for a period of 7 days. Extended treatment breaks may enable the tumor to recover and continue to grow; therefore, it is proposed to extend the duration of onvansertib treatment to 10 days in this study.

Figure 1 Onvansertib Concentration Over Time in the Colorectal Cancer Trial

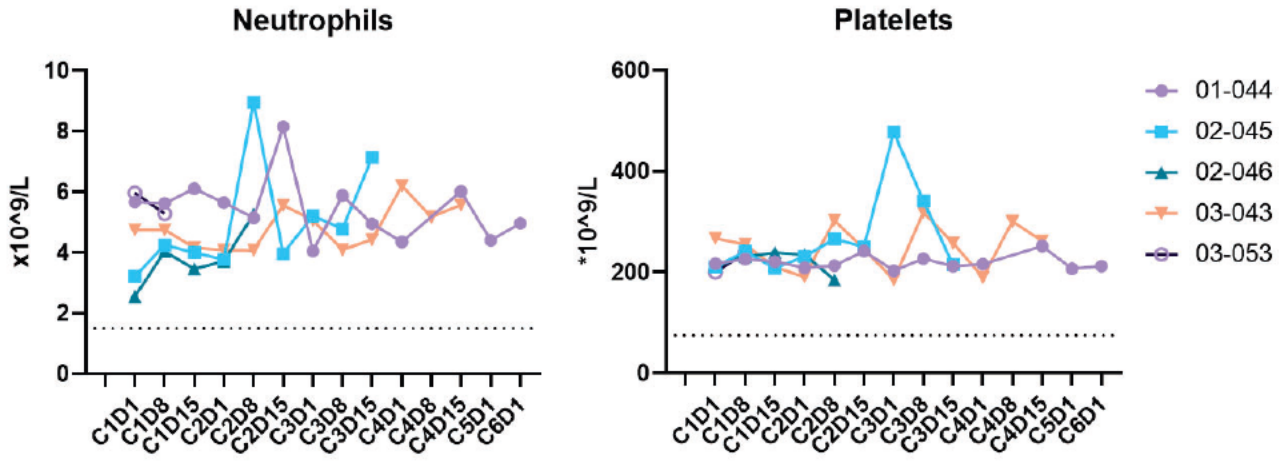


Abbreviations: IC_{50}=50% inhibitory concentration

A more continuous regimen of onvansertib is currently under clinical investigation in patients with mCRPC (NCT03414034). In this study, patients are treated with onvansertib 12 mg/m^2 QD for 14 days (Day 1 to Day 14) in combination with abiraterone QD in a 21-day cycle (14+7 regimen). As of 04 December 2020, 9 patients have been treated with this regimen, and no Grade 2 or higher hematological toxicities have been reported. While the completed onvansertib Phase 1 single agent study showed that neutropenia and thrombocytopenia were the primary on-target toxicities of onvansertib,[15] patients with mCRPC treated with onvansertib 12 mg/m^2 in a 14+7 regimen did not experience decreases in neutrophils and platelets (Figure 2). Together, these data indicate that prolonged exposure to onvansertib treatment at 12 mg/m^2 is safe and well tolerated. Of the 9 patients treated with onvansertib in the 14+7 regimen, 5 were evaluable for efficacy and 3 (60%) met the primary efficacy endpoint. In the alternative dosing regimen tested in the mCRPC study (5 days of onvansertib at 18 mg/m^2 in a 14-day cycle, [5+9 regimen]), 3 (30%) of the 10 evaluable

patients met the primary efficacy endpoint. Although preliminary, these data suggest that a regimen of more continuous dosing with onvansertib may increase efficacy.

Figure 2 Neutrophil and Platelet Counts in Over Time in the Metastatic Castration-resistant Prostate Cancer Trial



C=cycle; D=day.
Each line and number represent an individual patient in the metastatic castration-resistant prostate cancer trial.
Dotted line in the neutrophil graph represents threshold for Grade 1 neutropenia (1.5×10^9/L) and dotted line in the platelet graph represents threshold for Grade 1 thrombocytopenia (75×10^9/L).

Pharmacokinetic data from the completed onvansertib Phase 1 single agent study[15] was used to simulate onvansertib drug exposure in different dosing regimens. Onvansertib effective level threshold was calculated as 10 × the IC_{50} to account for effects of plasma protein binding. For evaluating drug exposure, maximum concentration (C_{max}), area under the curve from 0 to 336 hours ($AUC_{(0-336)}$), average concentration (C_{avg}; calculated as $AUC_{(0-336)}$/336 hours) and time above 10 × IC_{50} were calculated (Table 2). The simulations showed that while the C_{avg} of onvansertib was increased in the more continuous dosing regimens (12 mg/m^2 10+4 regimen or 14+7 regimen), the C_{max} was lower than for the 15 mg/m^2 5+9 regimen. Additionally, the time above 10 × IC_{50} during a 14-day period was increased in patients treated at 12 mg/m^2 for 10 days compared to patients treated at 15 mg/m^2 for 5 days (263 hours versus 148 hours, respectively). Therefore the 12 mg/m^2 10+4 regimen may result in a more profound and durable response in patients.

Table 2 Simulated Onvansertib Pharmacokinetic Results With Different Dose and Dosing Regimens

Onvansertib dose	Dosing schedule[a]	C_{max} (ng/mL)	C_{avg}[b] (ng/mL)	$AUC_{(0-336)}$ (ng*hr/mL)	Time above $10 \times IC_{50}$[c] (hr)
15 mg/m^2	5+9	223	61.9	20800	148
12 mg/m^2	10+4	179	99.1	33300	263
12 mg/m^2	14+7	179	133	44600	NA

Abbreviations: $AUC_{(0-336)}$=area under the curve from 0 to 336 hours; C_{avg}=average concentration; C_{max}=maximum concentration; IC_{50}=50% inhibitory concentration; QD=once daily.

[a] Dosing schedule represents number of days receiving onvansertib QD together with number of days not receiving onvansertib QD in any given treatment cycle. For example, a 5+9 dosing schedule represents onvansertib dosing QD on Day 1 to Day 5 of a 14-day treatment schedule.

[b] C_{avg} is calculated as $AUC_{(0-336)}/336$.

[c] $10 \times IC_{50}$ of onvansertib is calculated as 32.5 mg/mL to account for effects of plasma protein binding. Time above the $10 \times IC_{50}$ was calculated for a 14-day cycle.

2 STUDY DESIGN OBJECTIVES AND ENDPOINTS

This is a multicenter, open-label, single-arm study to assess the safety and preliminary efficacy of onvansertib in combination with nal-IRI, leucovorin, and 5-FU. Patients will have response assessment by Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) by computed tomography (CT) or magnetic resonance imaging (MRI) scan at 8-week intervals. Following each scan, only patients with disease control, defined as complete response (CR), PR, or SD, will continue on treatment until the occurrence of disease progression (PD), death, intolerance, withdrawal of consent, or inter-current illness, whereby the patient will be removed from the protocol treatment.

2.1 Objectives

2.1.1 Primary

- To assess the efficacy of onvansertib in combination with nal-IRI, leucovorin, and 5-FU for treatment of patients with histologically confirmed metastatic PDAC

2.1.2 Secondary

- To determine the OS of patients with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5-FU
- To determine the DOR of patients with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5-FU
- To assess the frequency and severity of adverse events (AEs) in patients with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5-FU

2.1.3 Exploratory

- To identify biomarkers related to sensitivity and resistance to treatment using patient-derived organoids, blood samples, and archival tissue biopsies.
- To assess KRAS allelic burden through serial collection of circulating tumor DNA (ctDNA) and to identify blood-based biomarkers related to: (a) de novo sensitivity and (b) tumor evolution and resistance

2.2 Endpoints

2.2.1 Primary

- Overall response rate (ORR) by RECIST v1.1.

2.2.2 Secondary

- Treatment safety based on toxicities evaluated according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 in patients who have received at least one dose of onvansertib

- Duration of response (DOR)
- ORR in patients who receive ≥ 2 treatment cycles of onvansertib, nal-IRI, leucovorin, and 5-FU
- Median OS
- Disease control rate (DCR; defined as CR, PR or SD) by RECIST v1.1 over the entire Treatment Period
- Reduction (≥50% from baseline) in serum CA 19-9 response

2.2.3 Exploratory

- Establishment of patient-derived organoids from tissue biopsies to perform pharmacosensitivity, genomic and transcriptomic analyses, and identify biomarkers associated with treatment response
- Genomic profiling of ctDNA at baseline and PD to identify genomic markers associated with patient sensitivity and resistance to treatment
- Use of archived tumor tissue biopsy samples (if available) to evaluate genomic profiles (DNA/RNA) associated with patient response
- Assessment of KRAS allelic burden in liquid biopsies as measured by ctDNA

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, open-label, single-arm study to assess the safety and preliminary efficacy of onvansertib in combination with nal-IRI, leucovorin, and 5-FU in patients with metastatic PDAC. PDAC patients must have histologically confirmed measurable and metastatic disease for study eligibility. In addition, patients must have failed treatment with one line of gemcitabine-based prior chemotherapy.

This study will consist of a Screening Period, a Safety Lead-in, a Treatment Period conducted in 14-day cycles, End-of-Study (EOS) evaluations, and a Follow-Up Period. The purpose of the Safety Lead-in is to assess the safety and tolerability of a modified onvansertib dose and dosing schedule of 12 mg/m^2 QD for 10 days in a 14-day treatment cycle. The safety and tolerability of the onvansertib 15 mg/m^2 QD for 5 days in a 14-day treatment cycle has been previously established. The recommended dose and regimen (either 12 mg/m^2 QD for 10 days in a 14-day treatment cycle or 15 mg/m^2 QD for 5 days in a 14-day treatment cycle) for the study will be determined in the Safety Lead-in based on the overall safety profile of each dose and dosing regimen, including dose-limiting toxicities (DLTs), drug modifications and reductions, and AEs.

Patients will continue treatment in this study (Cycle 1, Cycle 2, Cycle 3, etc.) until disease progression (PD) or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Prior to the start of each treatment cycle, patients will have blood samples drawn for hematology (see Section 6 for Schedule of Assessments). Only patients with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L will continue with study treatment for that cycle; patients not meeting this threshold will resume treatment when these criteria are met. Other non-hematological lab parameters should be within range per eligibility criteria (as defined in Table 3).

Local site-specific COVID-19-related procedures will be implemented to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the study.

3.1.1 Screening Period

Within 28 days prior to the first onvansertib (study drug) dose, Screening assessments will be performed, as outlined in the Schedule of Assessments (Table 6). Study procedures are outlined in detail in Section 6.

3.1.2 Safety Lead-in

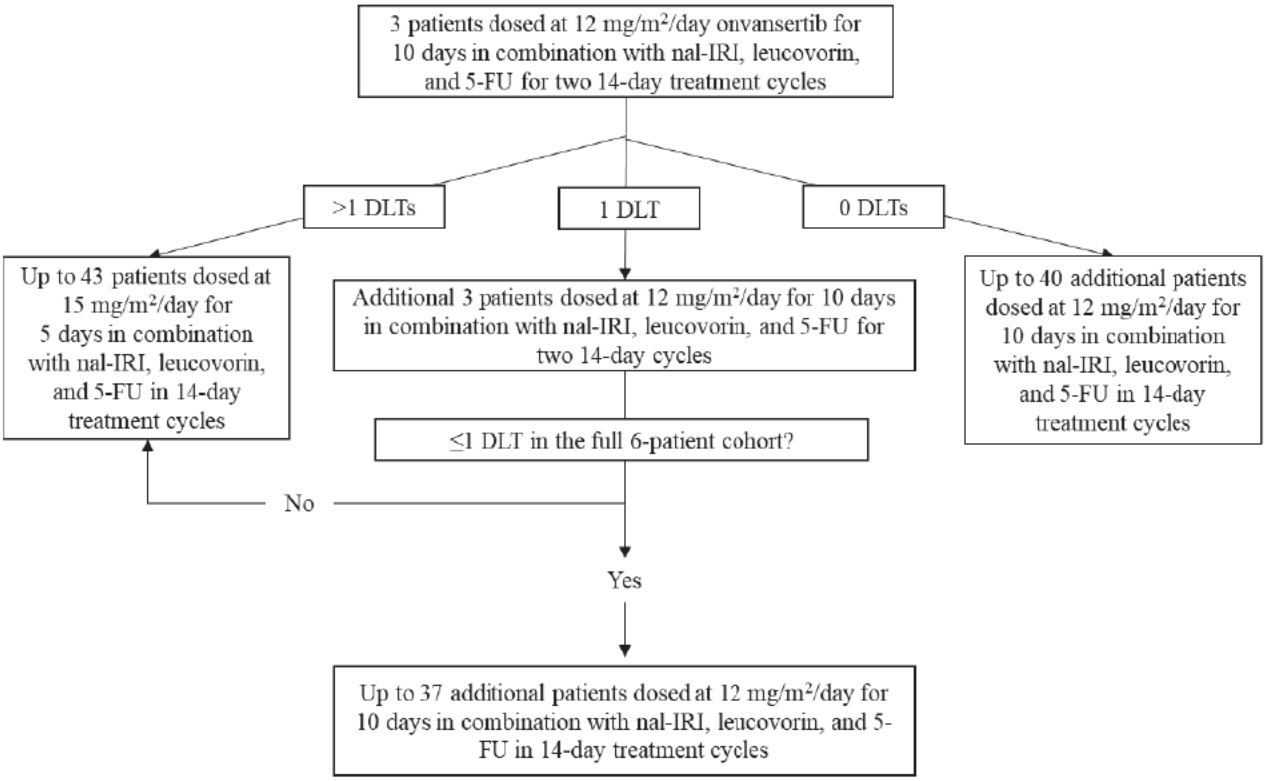
The purpose of the Safety Lead-in is to assess the safety and tolerability of a modified dose and dosing schedule for onvansertib. Three patients will initially be enrolled in the Safety Lead-in. On Day 1 of the first 2 cycles for the initial 3 patients in the Safety Lead-in, onvansertib will be administered PO QD at a dose of 12 mg/m^2 for 10 days (Day 1 to Day 10) of a 14-day cycle in combination with sequential administration of nal-IRI, leucovorin, and 5-FU.

The DLT evaluation period is the first two 14-day cycles of treatment plus an additional 2 weeks for any hematologic DLTs to resolve to Grade 2 or less or any nonhematologic DLT to resolve to

Grade 1 or less. Any Grade ≥ 3 adverse event, irrespective of drug attribution, is considered a DLT. At the end of the DLT evaluation period, safety data for the initial 3 patients will be reviewed by the Investigators and the Sponsor for evaluation of DLTs (see bulleted list below) or other safety events determined by the Investigators and Sponsor to be unacceptable. Depending on the results, the Safety Lead-in cohort may be expanded, or dosing of all subsequent patients in the trial will commence (see Figure 3):

- If no DLTs occur in the 3 first patients at a dose of 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) of the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, then dosing may begin for all subsequent patients at 12 mg/m^2 for 10 days (Day 1 to Day 10) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 40 additional patients would be enrolled.
- If 1 DLT is observed in the first 3 patients at a dose of 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) in the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, an additional 3 patients may be enrolled with the same dosing schedule, if deemed safe by the Sponsor and Study Investigators. If no further DLTs occur in these 3 additional patients, dosing may begin for all subsequent patients at 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) in the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 37 additional patients would be enrolled at the 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. However, if any further DLTs are observed in the 3 additional patients receiving 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) in the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, then all subsequent patients will be dosed at 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 43 patients would be enrolled at the 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU.
- If >1 DLT is observed in the first 3 patients at a dose of 12 mg/m^2 onvansertib for 10 days (Day 1 to Day 10) in the first two 14-day cycles in combination with nal-IRI, leucovorin, and 5-FU, then all subsequent patients will be dosed at 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) out of a 14-day cycle in combination with nal-IRI, leucovorin, and 5-FU. To reach the required sample size of up to 43 patients, up to 43 patients would be enrolled at the 15 mg/m^2 onvansertib for 5 days (Day 1 to Day 5) in combination with nal-IRI, leucovorin, and 5-FU.

Figure 3 Safety Lead-in Flow Chart



5-FU=fluorouracil; DLT=dose-limiting toxicity; nal-IRI=nanoliposomal irinotecan.

3.1.2.1 Definition and Management of DLTs

A DLT is defined as any grade ≥ 3 AE, irrespective of drug attribution. A DLT will result in a hold of drug until a hematologic DLT resolves to grade 2 or less or a nonhematologic DLT resolves to grade 1 or less. The DLT must resolve within 2 weeks or the patient will be discontinued from the study. The DLT evaluation period for patients in the Safety Lead-in is the initial two 14-day cycles, plus an additional 2 weeks for a hematologic DLT to resolve to Grade 2 or less, or a nonhematologic DLT to resolve to Grade 1 or less, if warranted. DLTs that occur during this time will result in additional patients accrued to Safety Lead-in and potentially dose modifications, as per the protocol (see Table 5 for dose reduction levels). DLTs are continually assessed throughout the treatment period and addressed per the protocol.

3.1.3 Treatment Period

Treatment will commence with the onvansertib dose selected based on the results of the Safety Lead-in (either 15 mg/m^2 administered orally (PO) on Day 1 to Day 5 of each 14-day cycle or 12 mg/m^2 administered PO on Day 1 to Day 10 of each 14-day cycle) in combination with nal-IRI 70 mg/m^2 (50 mg/m^2 in patients homozygous for UGT1A1*28), leucovorin 400 mg/m^2, and 5-FU 2400 mg/m^2 administered sequentially on Day 1 of each 14-day cycle.

Dose adjustments for onvansertib, nal-IRI, leucovorin, and 5-FU are allowed in accordance with Section 5.3; additional details for nal-IRI, leucovorin, and 5-FU are provided in the relevant package inserts.

Radiographic imaging during the Treatment Period will be obtained every 8 weeks, prior to the start of Cycles 5, 9, 13, 17, etc. until EOS as outlined in the Schedule of Assessments (Table 6). Radiographic imaging should include computed tomography (CT) of the chest/abdomen/pelvis with contrast (or magnetic resonance imaging [MRI] if patient has contraindication to intravenous contrast).

3.1.4 End-of-Study

The EOS visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered and should include the assessments outlined in the Schedule of Assessments (Table 6). The EOS visit is described further in Section 6.2.12.

3.2 Study Duration

The Screening Period will be up to 28 days prior to the first dose of onvansertib. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc.) until PD or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion.

4 STUDY POPULATION

4.1 Eligibility Criteria

Subjects who meet all of the following Inclusion Criteria and none of the Exclusion Criteria will be eligible to be enrolled in the study.

4.1.1 Inclusion Criteria

1. Histologically or cytologically confirmed metastatic PDAC
2. Has received 1 prior gemcitabine-based chemotherapy as first line therapy for metastatic disease. Progression after completion of neoadjuvant or adjuvant therapy of < 6 months in duration is considered 1 line of therapy for metastatic disease
3. Has measurable disease according to RECIST v1.1, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan
4. ECOG Performance Status 0-1
5. Must be willing and able to undergo a tissue biopsy at screening; patients who, in the opinion of the investigator, do not have tissue that is accessible for biopsy are excepted from this criterion
6. Women of childbearing potential: (defined as not post-menopausal for 12 months or no previous surgical sterilization) and fertile men must agree to use adequate contraception for the duration of study participation and for 4 months after the last dose of nal-IRI. Male subjects must agree to refrain from sperm donation during the study and for 4 months after the last dose of nal-IRI
7. Ability to understand and the willingness to sign a written informed consent document. Signed informed consent form must be obtained prior to initiation of study evaluations and/or activities
8. International Normalized Ratio (INR) < 1.5 unless on warfarin
9. Patients with prior malignancy and who were treated with no evidence of active disease more than 2 years from initial diagnosis are eligible
10. Age ≥ 18 years
11. Patients must have adequate organ and bone marrow function as defined in Table 3

Table 3 Definitions for Adequate Organ and Bone Marrow Function

ALT and AST	≤ 3 × institutional ULN OR ≤ 5 × ULN in presence of liver metastases
Bilirubin	≤ ULN
Creatinine	≤ 1.5 × ULN or creatinine clearance > 50 ml/minute as calculated by the Cockcroft-Gault equation
HGB	≥ 9.0 g/dL
ANC	≥ 1.5 × 10^9/L
PLTs	≥ 100 × 10^9/L

Abbreviations: ANC=absolute neutrophil count; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HGB=hemoglobin; PLTs=platelets; ULN=upper limit of normal.

4.1.2 Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Prior treatment with irinotecan, nal-IRI, or investigational PLK1 inhibitor
2. Uncontrolled intercurrent illness including symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, and myocardial infarction within 3 months of initiation of therapy
3. History of interstitial pneumonitis or interstitial lung disease
4. Patients with microsatellite instability-high (MSI-H) tumors with no prior immune checkpoint inhibitor exposure
5. Pregnancy or lactation
6. Patient has active and uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy
7. QT interval with Fridericia's correction (QTcF) > 470 milliseconds. The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation, (eg, medications, hypokalemia), the triplicate ECG may be repeated once during Screening and that result may be used to determine eligibility
8. Planned concomitant use of medications known to prolong the QT/QTc interval
9. Patient has undergone major surgical resection within 4 weeks prior to enrollment
10. Patient received radiotherapy, surgery, chemotherapy, or an investigational therapy within 2 weeks prior to study entry
11. Patient has serious medical risk factors involving any of the major organ systems such that the investigator considers it unsafe for the patient to receive an experimental research drugs
12. Serious psychiatric or medical conditions that could interfere with treatment
13. Major bleeding in the last 4 weeks

14. More than 1 prior chemotherapy regimen administered in the metastatic setting
15. Unable or unwilling to swallow oral medication
16. Use of strong CYP or UGT1A1 inhibitors or strong CYP inducers. Patients currently receiving these agents who are able to switch to alternate therapy are not excluded. Inhibitors should be stopped at least one week prior to the first dose of protocol therapy and inducers should be stopped at least two weeks prior to initiation of protocol therapy.

4.2 Removal of Patients From Therapy or Assessment

Patients will be discontinued from study drug administration for any of the following reasons:

- Intolerable toxicity as determined by the Investigator
- PD requiring an alternate therapy, in the opinion of Investigator
- Entry into another investigational clinical study or start of additional anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the Medical Monitor and/or Investigator
- Noncompliance with study procedures
- Patient withdrawal of consent or decision to discontinue participation
- Termination of the study by the Sponsor
- Any other reason that, in the opinion of the Investigator, would justify removal of the patient from the study

In the event that a patient is withdrawn from the study, every effort will be made by the Investigator to document and report the reasons for withdrawal as completely as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the patient's electronic Case Report Form (eCRF). An eCRF must be completed for any patient who receives study drug. An EOS reason must be recorded for any patient who receives study drug.

If a patient is discontinued from the study for any reason, every effort must be made to perform all EOS assessments (Section 6.1). In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record, and the missed visit should be reported as a deviation.

5 STUDY DRUG TREATMENT

5.1 Description

5.1.1 Onvansertib (PCM-075)

The chemical name of onvansertib (PCM-075H) is 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl] amino}-4,5-dihydro-1H-pyrazolo[4,3-h] quinazoline-3-carboxamide fumarate salt.

Onvansertib will be supplied as 5 mg and 20 mg (as free base) hard gelatin capsules that will be administered PO.

- A size 4 opaque caramel body and Swedish orange cap hard gelatin capsule contains 6.09 mg of onvansertib (PCM-075H) corresponding to 5 mg as free base, lactose monohydrate, pregelatinized starch and glyceryl behenate. The capsule body shell contains gelatin, black iron oxide, red iron oxide, yellow iron oxide and titanium dioxide; the capsule cap shell contains gelatin, red iron oxide and titanium dioxide.
- A size 4 opaque Swedish orange body and cap hard gelatin capsule contains 24.36 mg of onvansertib (PCM-075H) corresponding to 20 mg as free base, lactose monohydrate, pregelatinized starch and glyceryl behenate. The capsule shell contains gelatin, red iron oxide and titanium dioxide.

5.1.1.1 Storage

Onvansertib is stable at room temperature for up to 12 months. However, for optimal shelf-life, onvansertib is to be stored under refrigerated conditions (5°C ± 3°C; 36°F to 46°F) in the original packaging prior to usage. The research pharmacy may dispense onvansertib in standard pharmacy amber vials. Onvansertib does not need to be transported with ice packs, but once brought to a patient's home, it should be stored in a refrigerator, ideally within 24 hours.

5.1.1.2 Shelf-life

When onvansertib is stored at 5°C ± 3°C (36°F to 46°F), on the basis of the available stability information, a shelf-life of 48 months is currently assigned to the 5 mg and 20 mg (as free base) hard gelatin capsules.

Concurrent stability studies on the clinical batches are being conducted with 5 mg and 20 mg (as free base) hard gelatin capsules in order to evaluate the chemical, physical, and microbiological parameters. The onvansertib expiry date will be extended accordingly with the stability results. Any unexpected findings will be promptly communicated to Investigators and to the applicable regulatory authorities.

5.1.2 Nanoliposomal irinotecan

Packaging, labelling, and storage of nal-IRI will be in accordance with the prescribing information[18] and the Pharmacy Manual.

5.1.3 Leucovorin

Packaging, labelling, and storage of nal-IRI will be in accordance with the prescribing information[19] and the pharmacy manual.

5.1.4 Fluorouracil

Packaging, labelling, and storage of 5-FU will be in accordance with the prescribing information[20] and the Pharmacy Manual.

5.2 Administration

5.2.1 Onvansertib Administration

Administration should take place according to the time points outlined in the Schedule of Assessments (Table 6).

The starting dose of onvansertib will be either 15 mg/m^2 administered PO QD on Day 1 to Day 5 of every 14-day cycle or 12 mg/m^2 administered PO QD on Day 1 to Day 10 of every 14-day cycle. Dosing of onvansertib should be administered immediately prior to sequential administration of nal-IRI, leucovorin, and 5-FU.

5.2.1.1 Food Restrictions

Onvansertib should be administered after an overnight fasting, with free access to water. Drug should be taken with a large glass of plain water without ice. A light breakfast can be served 3 hours after drug intake.

5.2.1.2 Dose Rounding

Dose rounding is to the nearest 5 mg, rounded up for dose calculations ending in 0.5 to 0.9. For example, if 15 mg/m^2 dose is calculated at 32.4 mg, the dose would be rounded down to 30 mg, provided as one 20 mg capsule and two 5 mg capsules of onvansertib.

5.2.2 Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil Administration

Administration should be in accordance with the dose levels outlined in Table 4, and at the time points outlined in the Schedule of Assessments (Table 6). Dosing of each of these components should be sequential, ie, nal-IRI administered first, followed by leucovorin, then 5-FU. Detailed information for the individual drugs is available in the prescribing information.[18,19,20]

Table 4 Dose Levels of Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil

Drug	Dose	Frequency
Nanoliposomal irinotecan	70 mg/m^2 (50 mg/m^2 in patients homozygous for the UGT1A1*28 allele)	Day 1 of each 14-day cycle; 90-minute continuous IV infusion
Leucovorin	400 mg/m^2	Day 1 of each 14-day cycle; 30-minute continuous IV infusion
Fluorouracil	2400 mg/m^2	Beginning on Day 1 of each 14-day cycle; 46-hour continuous IV infusion

Abbreviations: IV=intravenous.

5.3 Dose Modifications

Patients who experience any Grade ≥ 3 AE (ie, adverse reaction or suspected adverse reaction according to the criteria in Section 7.3) will have their next doses of treatments held until all Grade ≥ 3 AEs have improved to Grade 1 or to Baseline. If the AE does not resolve to Grade 1 or less or to Baseline within 2 weeks, the patient will be discontinued from study treatment. Dose delays do not alter the Schedule of Assessments. If PK or pharmacodynamic studies are scheduled at the time of a dose delay, these will be delayed, and should be rescheduled by the Investigator and Sponsor.

Dose adjustments for onvansertib are allowed and are dependent on the initial dose level and regimen; any necessary dose reductions should be in accordance with the dose reduction levels presented in Table 5. Dose adjustments for nal-IRI and 5-FU are allowed, and any necessary dose reductions should be in accordance with the dose reduction levels presented in Table 5. Additional details for nal-IRI, leucovorin, and 5-FU are provided in the relevant package insert.[18,19,20]

Table 5 Dose Reduction Levels of Study Drugs

Drug	Starting Dose	Dose -1	Dose -2
Onvansertib	15 mg/m^2	12 mg/m^2	9 mg/m^2
	12 mg/m^2	9 mg/m^2	6 mg/m^2
Nanoliposomal irinotecan	70 mg/m^2	50 mg/m^2	43 mg/m^2
	50 mg/m^2 (for patients homozygous for the UGT1A1*28 allele)	43 mg/m^2 (for patients homozygous for the UGT1A1*28 allele)	35 mg/m^2 (for patients homozygous for the UGT1A1*28 allele)
Leucovorin	400 mg/m^2	no dose adjustment	no dose adjustment
Fluorouracil	2400 mg/m^2	1920 mg /m^2	1600 mg /m^2

For any Grade 1 and 2 nausea or vomiting, maximize the antiemetic regimen prescribed to the subject. For Grade 3 nausea or vomiting, reduce nal-IRI for the next cycle. For each subsequent cycle, the subject may continue nal-IRI at the previous dose level, provided nausea has resolved

to Grade 2 or 1. For Grade 4 nausea or vomiting, continue 5-FU infusion and nal-IRI at one lower dose level. If one of the drugs (onvansertib, nal-IRI, or 5-FU) must be discontinued based on Investigator discretion or due to toxicity, patients may continue to receive the other drug(s) alone.

If a patient forgets to take their dose of onvansertib on any day during Day 1 to Day 5 (if patients are dosed with 15 mg/m^2 onvansertib) or Day 1 to Day 10 (if patients are dosed with 12 mg/m^2 onvansertib) of the cycle, they will have the opportunity to take the scheduled dose within 4 to 6 hours of the original scheduled time on that same day. If a patient misses a dose of study drug on any day during Day 1 to Day 5 (if patients are dosed with 15 mg/m^2 onvansertib) or Day 1 to Day 10 (if patients are dosed with 12 mg/m^2 onvansertib) of the cycle, they will not be able to make up the missed dose on the next day or move the Day 1 to Day 5 or Day 1 to Day 10 dosing schedule out to additional consecutive days (eg, Day 6 or Day 11). If onvansertib is vomited, participants should not retake drug, but should take it instead at the next scheduled time.

5.4 Study Drug Inventory and Accountability

In accordance with current Good Clinical Practice (GCP), each study site will keep an accounting of all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the study site. Copies of the study drug accountability record will be provided to the Sponsor.

Study drug must only be dispensed to patients enrolled in the study and only as directed by this protocol. Administration of study drugs will be accurately recorded in each patient's source documents and eCRF.

5.5 Treatment Compliance

Compliance will be ascertained by Investigational Site staff by individual patient assessment and monitoring according to the site standard operating procedures. The Sponsor will provide a diary for patients to track their daily medication intake.

5.6 Concomitant Medications and Treatments

Concomitant medications are all medications (or treatments) other than study drugs that are taken or received by the patient at any time during the study starting at the time that the first dose of study drug was administered through the final study visit assessment. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the CRF.

All inter-current medical conditions will be treated at the discretion of the Investigator according to acceptable community and/or institutional standards of medical care.

The following medications are prohibited during the study:

- Investigational agents
- Other antineoplastic agents
- Radiotherapy

- Immunotherapy
- Strong CYP or UGT1A1 inhibitors or strong CYP inducers; inhibitors should be stopped at least one week prior to the first dose of protocol therapy and inducers should be stopped at least two weeks prior to initiation of protocol therapy

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Schedule of Assessments

The Schedule of Assessments is provided in Table 6.

Every attempt should be made to have each patient attend each visit as scheduled. Blood collection time points should be adhered to as closely as possible.

Table 6 Schedule of Assessments

Event	Screening ≤ 28 days prior to enrollment	On Treatment: 14-day cycles				End of Study[q]
		Day 1 (± 3 days, except Cycle 1)	Day 5 (± 3 days) (for patients taking 15 mg/m^2 onvansertib on Days 1-5 only)	Day 8 (± 3 days)	Day 10 (± 3 days) (for patients taking 12 mg/m^2 onvansertib on Days 1-10 only)	
Informed consent	X					
Confirmation of all eligibility criteria	X					
Medical history[a]	X					
Prior systemic and radiation therapy[b]	X					
Tumor biopsy[c]	X					
Physical examination[d]	X	X				X
ECOG performance status	X	X				X
Radiographic disease assessment[e]	X	X (prior to Day 1 of Cycle 5 and every 4th cycle thereafter)				X
Concomitant medication review	X	X				X
AE review	X	X				X
Triplicate 12-lead ECG (performed sequentially - no mandated time frame)[f]	X	X (Cycle 1 only; 3 hours after administration of onvansertib)	X (Cycle 1 and Cycle 3 only)		X (Cycle 1 and Cycle 3 only)	

Event	Screening ≤ 28 days prior to enrollment	On Treatment: 14-day cycles				End of Study[q]
		Day 1 (± 3 days, except Cycle 1)	Day 5 (± 3 days) (for patients taking 15 mg/m^2 onvansertib on Days 1-5 only)	Day 8 (± 3 days)	Day 10 (± 3 days) (for patients taking 12 mg/m^2 onvansertib on Days 1-10 only)	
Clinical chemistry[g]	X	X				
Hematology, including CBC with differential, and platelet count[g]	X	X		X (Cycles 1 and 2 only)		
CA 19-9 blood test[h]	X	X (prior to Day 1 of Cycle 5 and every 4th cycle thereafter)				X
Whole blood collection for UGT1A1 genotyping[i]	X					
Blood samples for PK assessment if patients receive 15 mg/m^2 onvansertib on Day 1 to Day 5 of a 14-day cycle[j]			X (Cycle 1 only, Days 5, 6, and 7)	X (Cycle 1 only)		
Blood samples for PK assessment if patients receive 12 mg/m^2 onvansertib on Day 1 to Day 10 of a 14-day cycle[j]					X (Cycle 1 only, Days 10, 11, 12, 13)	

Event	Screening ≤ 28 days prior to enrollment	On Treatment: 14-day cycles				End of Study[q]
		Day 1 (± 3 days, except Cycle 1)	Day 5 (± 3 days) (for patients taking 15 mg/m^2 onvansertib on Days 1-5 only)	Day 8 (± 3 days)	Day 10 (± 3 days) (for patients taking 12 mg/m^2 onvansertib on Days 1-10 only)	
Blood samples for ctDNA[k]		X (Cycle 1, 2, 3, and every other cycle after Cycle 3)				X
Onvansertib administration[l]		15 mg/m^2 on Days 1-5 QD PO **OR** 12 mg/m^2 on Days 1-10 QD PO				
Nal-IRI administration[m,n]		X				
Leucovorin administration[m,o]		X				
5-FU administration[m,p]		X				

Abbreviations for Table 7 and footnotes: 5-FU=fluorouracil; AE=adverse event; ANC=absolute neutrophil count; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group (performance score); ECG=electrocardiograms; EOS=End-of-Study; MRI=magnetic resonance imaging; nal-IRI=nanoliposomal irinotecan; PK=pharmacokinetic; PO=orally; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; TNM=tumor, lymph nodes, metastasis.

[a] Medical history: including relevant medical history collection as well as TNM stage at diagnosis.
[b] For radiation treatment, collect radiation site, administered dose per fraction and treatment duration.
[c] Collection of tumor tissue from endoscopic ultrasound guided fine-needle biopsy (EUS-FNB), percutaneous core-needle biopsy (PCNB) or other types of needle/core biopsies will be obtained at screening for the establishment of patient-derived organoids. Tissue biopsy is mandatory for all patients except those who, in the opinion of the investigator, do not have tissue that is accessible for biopsy.
[d] Physical examination includes height (at screening only), weight, vital signs, and general physical examination.
[e] Radiographic disease assessment by CT and MRI using RECIST v1.1 will be performed at screening, then every 8 weeks after starting treatment (prior to Day 1 of Cycle 5 and every 4th cycle thereafter [prior to Day 1 of Cycles 9, 13, 17, 21, etc.]), and at EOS. Assessment can be performed up to 7 days before Day 1 of the indicated cycles.

[f] Triplicate ECGs should be recorded 3 hours after onvansertib administration on Day 1 of Cycle 1. For patients taking 15 mg/m^2 onvansertib on days 1 to 5 of the 14-day treatment cycle, triplicate ECGs should be obtained on Day 5 of Cycle 1 and Cycle 3; for patients taking 12 mg/m^2 onvansertib on days 1 to 10 of the 14-day treatment cycle, triplicate ECGs should be obtained on Day 10 of Cycle 1 and Cycle 3. Additional ECGs can be obtained periodically during treatment as clinically indicated.

[g] Blood chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, AST, ALT. Only patients with ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L on Day 1 of each cycle will continue with study treatment for that cycle; patients not meeting this threshold will resume treatment when these criteria are met. Other non-hematological lab parameters should be within range per eligibility criteria (as defined in Table 3). Hematology at Day 8 will be collected only for the first 2 cycles.

[h] CA 19-9 blood test will be performed concomitant to radiographic imaging at screening, then every 8 weeks after beginning of treatment (prior to Day 1 of Cycle 5 and every 4th cycle thereafter [prior to Day 1 of Cycles 9, 13, 17, 21, etc.]), and at EOS.

[i] Whole blood will be collected for UGT1A1 genotyping. Patients homozygous for the UGT1A1*28 allele will receive 50 mg/m^2 nal-IRI as a starting dose. Patients not homozygous for the UGT1A1*28 allele will receive 70 mg/m^2 nal-IRI as a starting dose.

[j] Blood samples for PK analysis will be obtained during Cycle 1 only, on Days 5, 6, 7, and 8 if patients are dosed with 15 mg/m^2 onvansertib on Days 1 to 5 of a 14-day cycle, or on Days 10, 11, 12, and 13 if patients are dosed with 12 mg/m^2 onvansertib on Days 1 to 10 of a 14-day cycle. Samples on Day 5 (if patients are dosed with 15 mg/m^2 onvansertib on Days 1 to 5 of a 14-day cycle) or Day 10 (if patients are dosed with 12 mg/m^2 onvansertib on Days 1 to 10 of a 14-day cycle) should be collected pre-dose and 1, 2, 3, 4, and 8 hours post dose; samples on other days should be collected 24, 48, and 72 hours after the last dose in Cycle 1.

[k] Blood for ctDNA assessment will be collected in three 10-mL Streck tubes on Day 1 of Cycles 1, 2, and 3, and on Day 1 of every other cycle after Cycle 3 (Cycles 5, 7, 9, 11, etc), and at EOS. ctDNA samples may be collected any time before dosing.

[l] Patients will either take 15 mg/m^2 onvansertib QD PO on Day 1 to Day 5 of each 14-day treatment cycle or 12 mg/m^2 onvansertib QD PO on Day 1 to Day 10 of each 14-day treatment cycle, depending on the outcome of the Safety Lead-in. Onvansertib will be dosed in the clinic on Day 1 of each 14-day treatment cycle but otherwise will be taken at home. Administration of onvansertib should occur concurrently with nal-IRI, leucovorin, and 5-FU on Day 1 of each treatment cycle.

[m] Dosing of nal-IRI, leucovorin, and 5-FU should be sequential; nal-IRI administered first, followed by leucovorin, and lastly 5-FU.

[n] Nal-IRI should be given on Day 1 of each 14-day treatment cycle in a 90-minute infusion. The starting dose for nal-IRI is dependent on the results of the UGT1A1 genotyping: for patients homozygous for the UGT1A1*28 allele the starting dose will be 50 mg/m^2; for patients not homozygous for the UGT1A1*28 allele the starting dose will be 70 mg/m^2.

[o] Leucovorin should be given on Day 1 of each 14-day treatment cycle in a 30-minute infusion.

[p] 5-FU should be given on Day 1 of each 14-day treatment cycle in a 46-hour infusion.

[q] Assessments should be conducted within 28 days (±5 days) after the last dose of onvansertib. Follow-up information will be collected via voice or written contact for up to 1 year approximately every 8 weeks for disease progression and for survival.

6.2 Study Procedures

Descriptions of assessments are provided in Sections 6.2.1 through 6.2.12, below. Specific timing requirements for study assessments and procedures are provided in Table 6.

6.2.1 Informed Consent and Confirmation of Eligibility Criteria

Patients must be able to provide written informed consent and meet all eligibility criteria (refer to Section 4.1) prior to enrollment.

6.2.2 Screening

The Investigator is responsible for keeping a record of all patients screened for entry into the study and those that are subsequently excluded. The reason(s) for patient exclusion from the study must also be recorded.

Each patient (or patient's legal representative if applicable) must provide written informed consent before any study specific assessments may be performed.

Screening assessments should be performed in accordance with the Schedule of Assessments (Table 6).

6.2.3 Medical History and Prior Therapy

Medical history includes a thorough review and recording of significant past medical and surgical history, current conditions, concomitant therapies, and TNM stage at diagnosis.

Demographics including age, gender, race, and ethnicity will be recorded.

Prior treatments should be recorded with start and end dates. If there was intolerance, the reason should be recorded. For prior radiation therapy, radiation site, administered dose per fraction, and treatment duration should be recorded.

6.2.4 Tumor Biopsy

Collection of tumor tissue from endoscopic ultrasound guided fine-needle biopsy (EUS-FNB), percutaneous core-needle biopsy (PCNB) or other types of needle/core biopsies will be obtained at screening for the establishment of patient-derived organoids. Tissue biopsy is mandatory for all patients except those who, in the opinion of the investigator, do not have tissue that is accessible for biopsy.

6.2.5 Physical Examinations, Height and Weight, and Vital Signs

A complete physical examination should be conducted including height (at Screening only), weight, vital signs, and general physical examination. A limited physical examination (e.g., symptom-directed examination of specific organ systems/body area) should be conducted at the specified time points after screening in accordance with the Schedule of Assessments (Table 6).

6.2.6 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed in all patients in accordance with the Schedule of Assessments (Table 6). The ECOG performance is provided in Appendix 16.2. The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

6.2.7 Radiographic Disease Assessment

Radiographic imaging (CT and MRI) will be performed as outlined in Schedule of Assessments (Table 6). Radiographic imaging may occur up to 28 days prior to administration of the first dose of onvansertib.

6.2.8 Concomitant Medication Review

Concomitant medications should be recorded in accordance with the Schedule of Assessments (Table 6).

All medications that were used from 28 days prior to enrollment through the end of study participation will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 4.1.2). Additional guidance regarding concomitant medication is provided in Section 5.6.

6.2.9 Adverse Events

Adverse events should be collected/recorded in accordance with the Schedule of Assessments (Table 6).

Detailed guidance for AE reporting is provided in Section 7.

6.2.10 Electrocardiograms

Twelve-lead electrocardiograms (ECGs) will be performed in triplicate in accordance with the Schedule of Assessments (Table 6). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. Any clinically significant changes in ECGs that occur during the study should be reported as AEs in the eCRF. ECGs can be obtained periodically during treatment as clinically indicated.

6.2.11 Laboratory Assessments

6.2.11.1 Chemistry

Blood samples should be collected for clinical chemistry laboratory testing in accordance with the Schedule of Assessments (Table 6). The blood chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose,

albumin, alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Clinical chemistry testing may occur up to 48 hours prior to Day 1. All visits have a ± 3-day window.

6.2.11.2 Hematology

Blood samples for hematology laboratory testing, including complete blood count (CBC) panel, with differential and platelet count should be collected in accordance with the Schedule of Assessments (Table 6). Only patients with ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L on Day 1 of each treatment cycle (prior to treatment) will continue with study treatment for that cycle; patients not meeting this threshold will resume treatment when these criteria are met. CBC may occur up to 48 hours prior to Day 1.

6.2.11.3 Samples for Pharmacokinetic Analysis

Blood samples for PK analysis should be obtained during Cycle 1 only on Days 5, 6, 7, and 8 if patients are dosed with 15 mg/m^2 onvansertib on Days 1 to 5 of a 14-day cycle, or on Days 10, 11, 12, and 13 if patients are dosed with 12 mg/m^2 onvansertib on Days 1 to 10 of a 14-day cycle in accordance with the Schedule of Assessments (Table 6).

6.2.11.4 Samples for Circulating Tumor DNA

Blood samples for ctDNA assessment should be collected prior to study treatment administration and at the time points outlined in the Schedule of Assessments (Table 6). Blood will be collected in three 10-mL Streck tubes.

6.2.12 End-of-Study/Follow-Up

The EOS visit should occur within 28 days after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6).

Follow-up information will be collected via voice or written contact approximately every 8 weeks for PD and for survival for up to 1 year.

Any patient with a suspected study drug-related toxicity at the last follow-up visit must be followed until resolution or until the event is considered irreversible. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded on the appropriate page of the CRF, and in the patient's source documentation.

7 ADVERSE EVENT REPORTING

7.1 Definitions

7.1.1 Adverse Event

An AE is defined in Title 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.2 Unexpected Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

- An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in patient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2 Severity of Adverse Events

Each AE will be graded according to the NCI-CTCAE version 5.0 (Appendix 16.1). In most cases AE terms will be listed in the CTCAE, with grading criteria specific to that term. If the AE is not specifically defined in the CTCAE, it is to be reported using the "Other, specify" term under the appropriate system organ class and graded according to the general CTCAE severity guidelines.

7.3 Relationship of Adverse Events to the Study Drug

The Investigator must attempt to determine if an AE is in some way related to the use of the onvansertib. This relationship should be described as follows:

- **Unrelated:** The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease or circumstance.
- **Unlikely:** The event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- **Possibly:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug, BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication.
- **Probably:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication.
- **Definitely:** The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

7.4 Monitoring of Adverse Events

AEs will be monitored continuously during the study starting immediately after the first dose of study drug is administered. Patients will be instructed to report all AEs experienced during the study, and patients will be assessed for the occurrence of AEs throughout the study.

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

7.5 Reporting Procedures

7.5.1 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded on the AE form of the CRF and will be submitted to the Sponsor at regularly scheduled intervals.

The information to be entered in the CRF will include:

1. Time of onset of any new AE or the worsening of a previously observed AE. In most cases, date of onset will be adequate; however, for days when the patient is in the clinic and receives study drug, the time (based on a 24-hour clock) of onset should also be recorded
2. Specific type of reaction in standard medical terminology
3. Time of resolution of the event (or confirmation ongoing). In most cases, date of resolution will be adequate; however, for events that initiate and resolve on days where the patient is in the clinic and receives study drug, the time (based on a 24-hour clock) of resolution should also be recorded
4. Severity/grade of AE. The severity should be rated according to NCI-CTCAE version 5.0 (Appendix 16.1)
5. An assessment should be made of the relationship of the AE to the study drug according to the definitions outlined in Section 7.3.
6. Description of action taken in treating the AE and/or change in study drug administration or dose

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

7.5.2 Reporting of Serious Adverse Events, Including Death

Serious adverse events, including death due to any cause, that occur during this study or within 30 days following the last dose of the study drug, whether or not related to the administration of study drug, must be reported to the Medical Monitor by telephone or email **within 24 hours of learning of the event**.

Serious adverse event forms will be provided by the Sponsor or Sponsor Designated Contract Research Organization (CRO). The study site should send the SAE Form to the Medical Monitor as soon as possible so that the tracking procedure can begin immediately upon receipt of the information. Once the Medical Monitor is informed of an SAE with preliminary information obtained, the study site will be instructed to update the SAE Form with additional information, according to the following guidelines:

If all information is not known at the time of the incident, an initial report should still be made. In the event there is a question as to whether the event is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Medical Monitor. In the case of fatality, autopsy reports will be furnished to the Medical Monitor as soon as available.

During the initial communication, the Medical Monitor will require the following information about the patient and the reported SAE:

1. Patient identification including patient number, initials, and date of birth
2. Date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose
3. Date of last dose of study drugs (i.e., prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer, lot number, expiration date, and dose)
4. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event)
5. Date of onset of the AE
6. Date of resolution of the AE (or confirmation ongoing)
7. Severity of the AE (refer to Section 7.2)
8. Assessment of the attribution of the AE to the study drug (refer to Section 7.3)
9. Reason AE is considered serious (according to definition in Section 7.1.3)
10. Whether the AE is expected (refer to Section 7.1.2)
11. Action taken in treating the AE and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the patient was discontinued from the study)
12. All concomitant medications (including doses, routes, regimens, and indications)
13. Pertinent clinical laboratory testing data
14. Medical history

The Investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the adverse experience to study drugs and to underlying disease. Based on the Investigator's and Medical Monitor's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol
2. Discontinuation or suspension of the study
3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings
4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study drug-related.

Any SAE that is determined by the Sponsor to be reportable to Food and Drug Administration (FDA) as an Investigational New Drug (IND) Safety Report [as defined in 21 CFR 312.32] will be reported to FDA by the Sponsor within the specified time frame. All IND Safety Reports will

also be promptly provided to the Investigator for submission to his or her Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor within the specified time frames, and will be provided to the Investigator for submission to his or her IRB/IEC.

7.5.3 Other Events Requiring Immediate Reporting

7.5.3.1 Overdose

An overdose is defined as a patient receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol. Any overdose of a study patient with the investigational product, with or without associated AEs/SAEs, is required to be reported to the Medical Monitor within 24 hours of knowledge of the event. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

7.5.3.2 Pregnancy

Should the Investigator become aware of a pregnancy of a female partner of a participant, the pregnancy should be reported within 24 hours of knowledge of the event. After obtaining the patient's consent (or patient and pregnant partner's consent in the case of a male participant), monitoring of the pregnancy and infant should comply the following procedures:

- If the outcome is an abnormal neonate (infant), as much follow up information as possible to permit evaluation of the case will be collected, including where possible, medical confirmation, medical investigations and medical record summary details. Follow up should continue for at least 1 year post birth.
- If the outcome is a normal neonate, follow up data should continue for 1 month

8 PATIENT DISCONTINUATION AND TRIAL DISCONTINUATION

8.1 Patient Discontinuation

A patient may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled.

Patients will be discontinued from study drug (onvansertib) treatment if one or more of the following events occur:

1. Clinically significant PD
2. Patient refusal to remain on study
3. Non-compliance or inability to comply with protocol requirements by patient
4. Development of unacceptable toxicity (regardless of study drug relationship)
5. Determination by the Investigator that it is no longer safe for the patient to continue therapy.

Patients who have an ongoing AE at the time of discontinuation will continue to be followed until resolution of the event to Grade ≤ 1 or baseline, or until the event is considered irreversible.

8.2 Study Discontinuation

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation between involved parties. The Investigator must notify the IRB/IEC in writing of a premature termination of a study or closure of Investigational Site, and must send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the study from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

9 STATISTICAL METHODS

9.1 Determination of Sample Size

The total planned sample size is up to 43 patients. The primary endpoint is ORR by RECIST v1.1.

9.2 Statistical Considerations

The primary endpoint will be tested, and a Fleming single-stage design will be used.[21] The null hypothesis for ORR that the true ORR is 7.7% will be tested against a one-sided alternative of 20% ORR.

The null hypothesis on ORR will be rejected if 6 or more responses are observed in the first 39 evaluable patients. For the primary endpoint, the sample size will provide 80% power to reject the alternative hypothesis with type I error rate of 0.1 (actual error rate of 0.076; PASS 14 Power Analysis and Sample Size Software v14.0.05). Evaluable patients are defined as those who receive at least 1 cycle of onvansertib in combination with 5-FU, leucovorin, and nal-IRI. Four additional patients will be enrolled to take into account ineligibility, withdrawals, etc.

9.3 Statistical Analysis

9.3.1 Statistical Analysis of Safety Data

Data from all patients who receive at least 1 dose of the study drugs will be included in the safety analysis.

Safety will be assessed primarily based on AEs. The severity of AEs will be graded as mild, moderate, severe, or life-threatening according to NCI-CTCAE version 5.0 (Appendix 16.1). Other safety assessments will include data from concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, and clinical laboratory testing values. Descriptive statistics will be generated as appropriate (eg, mean, median, range, and standard deviation for continuous data; and frequency for categorical data).

9.3.2 Statistical Analysis for Efficacy Data

The primary endpoint is ORR by RECIST v1.1. Subjects who had received at least 1 cycle of the study drugs will be included in the treated-patient population efficacy analysis.

Descriptive statistics will be generated as appropriate (eg, mean, median, range, and standard deviation). Median survival statistics will be estimated using the Kaplan-Meier method.

9.3.3 Statistical Analysis for Pharmacodynamics and Biomarkers

ctDNA isolated from serial blood samples will be used to monitor changes during treatment and will be correlated with patient response.

Genomic profiles (RNA and/or DNA) will be performed on ctDNA, patient-derived organoids, and biopsy tissue (if available) to evaluate biomarkers correlated with patient response.

Pharmacosensitivity to onvansertib, 5-FU, leucovorin, and nal-IRI will be assessed in patient-derived organoids and correlated to treatment response.

10 ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this study available for monitoring by the Sponsor or its representatives, or by regulatory authorities or health authority inspectors.

Patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB/IEC.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study drug and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical Investigators, to other pharmaceutical companies, to the FDA and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region (i.e., US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the patient, appropriate copies for storage off-site will be made.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Collection

All data required by the study protocol will be entered onto eCRFs and must be verifiable against source documents. eCRFs will be completed for every patient who is enrolled in this study.

Only authorized Investigational Site personnel will enter data on the eCRFs. Any corrections to data entered into the eCRF will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The eCRFs will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and eCRF entries and will sign and date each patient's eCRF, verifying that the information is true and correct.

11.2 Study Monitoring

The study will be monitored to evaluate the progress of the study, to verify the accuracy and completeness of the eCRFs, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The Investigator will allow the study monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each patient in the study.

The study monitor will compare the eCRF data against source documentation in order to verify its accuracy and completeness. The Investigator and research staff will collaborate with the study monitor to resolve any identified data discrepancies in a timely manner.

The study monitor will record any protocol deviations identified, including, but not limited to, patients that were enrolled even though they did not meet all eligibility criteria, patients who took concomitant medications specifically prohibited by the protocol (refer to Section 5.6), and patients who received the wrong study drug or incorrect dose. The Investigator and research staff will collaborate with the study monitor to identify the reason for each protocol deviation.

The study monitor will compare the Investigational Site study drug accountability record against the study drug inventory (unused and used) at the site. The Investigator and research staff will collaborate with the study monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

11.3 Data Management

After the CRFs have been reviewed by the study monitor and all identified discrepancies have been identified, the Investigator signed copy of the eCRFs will be forwarded to the CRO for the study, Data Management. The CRO is responsible for data and safety monitoring. Queries

generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses.

All CRF data will be entered into a validated database and an electronic audit study of edits maintained. Laboratory data may be imported to the database electronically.

The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

11.4 Sponsor Audits

At some point during the study, individuals from the Sponsor's Quality Assurance group or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff will cooperate with the auditors and allow access to all patient records supporting the CRFs and other study-related documents.

11.5 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

12 ETHICS

12.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki.

12.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical studies and the protection of human patients.

12.3 Institutional Review Board/Independent Ethics Committee

The protocol, informed consent form (ICF), IB, and any materials (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to initiation of the study.

Amendments to the protocol will be patient to the same requirements as the original protocol. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to implementation of the changes described in the protocol amendment.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB/IEC by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

12.4 Informed Consent

No study related procedures, including Screening evaluations, will be performed until the patient has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the patient understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will provide the Sponsor with a letter documenting the IRB/IEC approval prior to initiation of the study.

The IRB/IEC-approved ICF will be given to each prospective participant. The patients will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the study and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the patient to use and/or disclose Protected Health Information in compliance with Health Insurance Portability and Accountability Act (HIPAA) or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the patient, or the known risks of the study drug change during the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised ICF must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment and to obtain consent from new patients prior to enrollment.

12.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that patient. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor's Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the patient (for whom the departure from protocol was affected) is to continue in the study. The CRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

13 PUBLICATION POLICY

All information and data obtained during the study are the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical study agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

14 PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving Sponsor authorization to do so, except in those cases intended to reduce immediate risk of the patients. The Sponsor is responsible for submitting protocol amendments to the appropriate governing regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB/IEC. Approval by the IRB/IEC will be obtained before protocol modifications are implemented, except in those cases intended to reduce immediate risk to patients.

15 REFERENCES

1. Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362(17):1605-17.
2. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691-703.
3. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817-25.
4. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
5. Wang-Gillam A, Li C-P, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387:545-57.
6. Waters AM, Der CJ. KRAS: The Critical Driver and Therapeutic Target for Pancreatic Cancer. Cold Spring Harb Perspect Med 2018;8(9).
7. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012;491(7424):399-405.
8. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518(7540):495-501.
9. Degenhardt Y, Lampkin T. Targeting Polo-like kinase in cancer therapy. Clin Cancer Res 2010;16(2):384-9.
10. Knecht R, Elez R, Oechler M, et al. Prognostic significance of polo-like kinase (PLK) expression in squamous cell carcinomas of the head and neck. Cancer Res 1999;59(12):2794-7.
11. Weichert W, Kristiansen G, Schmidt M, et al. Polo-like kinase 1 expression is a prognostic factor in human colon cancer. World J Gastroenterol 2005;11(36):5644-50.
12. Weichert W, Kristiansen G, Winzer KJ, et al. Polo-like kinase isoforms in breast cancer: expression patterns and prognostic implications. Virchows Arch 2005;446(4):442-50.
13. Luo J, Emanuele MJ, Li D, et al. A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell 2009;137(5):835-48.
14. Wang J, Hu K, Guo J, et al. Suppression of KRas-mutant cancer through the combined inhibition of KRAS with PLK1 and ROCK. Nat Commun 2016;7:11363.
15. Weiss GJ, Jameson G, Von Hoff DD, et al. Phase I dose escalation study of NMS-1286937, an orally available Polo-Like Kinase 1 inhibitor, in patients with advanced or metastatic solid tumors. Invest New Drugs 2018;36(1):85-95.
16. Drummond DC, Noble CO, Guo Z, et al. Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. Cancer Res 2006;66(6):3271-7.
17. Ahn DH. A phase Ib/II study of the polo-like kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC)2020; ASCO Virtual Scientific Program. American Society of Clinical Oncology.
18. Onivyde [package insert]. Cambridge (MA): Merrimack Pharmaceuticals Inc.; 2015.

19. Leucovorin Calcium Injection USP [package insert]. Bedford (OH): Ben Venue Laboratories, Inc.; 2011.
20. Fluorouracil [package insert]. Irvine (CA): Spectrum Pharmaceuticals Inc.; 2016.
21. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982;38(1):143-51.

16 APPENDICES

16.1 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

NCI-CTCAE version 5.0 will be used in this study for AE reporting.

A copy of CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP).

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

16.2 Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Note: As previously published.